REMARKS

Claims 1-33 are pending in the application. Claims 1-4, 8, 9, and 12-33 stand rejected. Claims 5-7 and 10-11 have been withdrawn due to the election of species requirement with the understanding that additional species will be considered upon the allowance of a generic or linking claim. Claims 1, 2, 3, and 33 have been amended. Claims 34-67 have been canceled. New Claims 68-70 have been added. Reconsideration and allowance of Claims 1-4, 8, 9, 12-33, and 68-70 in view of the following remarks is respectfully requested.

The Rejection of Claims 1-33 Under 35 U.S.C. § 101 as Being Directed to Non-Statutory Subject Matter

With regard to Claims 1-32, the Examiner has taken the view that there is no step of physical transformation and that the claims do not produce a tangible result. Without acquiescing to the Examiner's position, but in order to facilitate prosecution, Claim 1, from which Claims 2-29 depend, has been amended to clarify the invention and recites "(a) obtaining an expression measurement of at least one gene population or at least one protein population in living cells contacted with an agent and generating at least one of an efficacy value of the agent, a toxicity value of the agent or a classifier value of the agent . . . ."

It is submitted that Claim 1, as amended, is in compliance with 35 U.S.C. § 101 at least because the method includes a physical transformation of obtaining an expression measurement of at least one gene population or protein population in living cells with an agent and generating at least one of an efficacy value of the agent, a toxicity value of the agent or a classifier value of the agent. In addition, it is noted that the claimed invention produces a useful, concrete and tangible result, as required under M.P.E.P. 2107. For example, as described in the specification, the methods of the invention have been used to identify PPARγ agonists and/or PPARγ partial agonists. See specification at page 62, line 15, to page 64, TABLE 3.

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Claim 33 has been amended to recite "an isolated population of oligonucleotide probes," as suggested by the Examiner.

Accordingly, removal of the rejection of Claims 1-33 under 35 U.S.C. § 101 is respectfully requested.

The Rejection of Claims 1-4, 12-16, 28, and 30-32 Under 35 U.S.C. § 102(b) as Being Anticipated by WO 02/059560 (Castle et al.)

Claims 1-4, 12-16, 28, and 30-32 stand rejected under 35 U.S.C. § 102(b) as being anticipated by WO 02/059560 (Castle et al.). Applicants traverse the rejection for the following reasons.

Without acquiescing to the Examiner's position, but in order to facilitate prosecution, Claim 1 (from which Claims 2, 3, 4, 12-16, 28, and 30-32 depend) has been amended to clarify the invention and now recites at step (c) "using the comparison result(s) obtained in step (b) to determine whether the agent possesses the defined biological activity and to determine the degree of the defined biological activity."

Support for this amendment is found throughout the specification as filed, for example at page 25, lines 16, to page 26, line 3; page 35, line 4, to page 44, line 25; Example 1; Table 3.

It is respectfully submitted that Castle et al. does not anticipate the claimed invention as amended. In order to anticipate, the reference must disclose, either expressly or inherently, each and every element of the claim. M.P.E.P. 2131.

Castle et al. is directed to the use of a toxicological algorithm using a logistic regression (binary) method to provide a predictive model regarding the toxicity of a substance. As described in Castle et al., the logistic regression analysis only deals with *a binary categorical outcome* (*e.g.*, only 0 to 1, toxic or not). For example at page 9, lines 10-16, Castle et al. states:

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> [t]he summary scores are subjected to logistic regression analysis, resulting in a predictive model. In this aspect of the embodiment, the input data are the summary scores per sample, which is an indicator for each sample; the analysis is a logistic regression analysis mapping the summary scores to a 0 to 1 scale of toxicity, and the out put data are one or more mathematical formulae that converts a column of average differences into *a single 0 to 1 toxicological score* for a sample.

(Emphasis added).

In sharp contrast to the teachings of Castle et al., the claimed invention is directed to comparing at least one of an efficacy value of an agent, a toxicity value of an agent or a classifier value of an agent to at least one of a reference efficacy value, a reference toxicity value or a reference classifier value to determine whether the agent possesses the defined biological activity and to determine the *degree of the defined biological activity*. Therefore, in contrast to the teachings of Castle et al, which are directed to logistic regression resulting in a binary categorical outcome, the methods of the invention are used to obtain a *continuous outcome* (*e.g.*, through the use of chi-square fitting approach to generate interval/ratio data), which allows for the computation of a degree of biological activity in order to identify agents that possess a desired therapeutic profile with regard to efficacy and/or toxicity. For example, the methods of the claimed invention may be used to identify glucose lowering agents that have activity ranging from full agonist to partial agonist, weak agonist activity, or no agonist activity. See, *e.g.*, Example 1, page 57, line 19, to page 64, line 3; and Table 3.

Therefore, it is respectfully submitted that the teachings of Castle et al., fail to anticipate or suggest the methods of the claimed invention, as amended. Removal of this ground of rejection is respectfully requested.

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The Rejection of Claims 1, 8, 9, 13, 16-17, 27, and 29 Under 35 U.S.C. § 103(a) as Being Unpatentable Over WO 02/059560 (Castle et al.) in View of Mukherjee et al. (*Molecular Endocrinology 14*(9):1425-1433 (2000))

Claims 1, 8, 9, 13, 16-17, 27, and 29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 02/059560 (Castle et al.) in view of Mukherjee et al. (*Molecular Endocrinology 14*(9):1425-1433 (2000)). The Examiner characterizes Castle et al. as disclosing the use of linear regression to compare the reference toxicity of a substance to toxicity as time progresses. The Examiner has taken the view that the model of Castle et al. is used not only to determine agent toxicity, but also agent efficacy, by assigning the agent a classification such as that shown in Figure 1 of Castle et al. The Examiner acknowledges that Castle et al. does not teach partial agonist activity with respect to a biological response, partial agonist activity with respect to PPARγ, use of 3T3L1 adipocyte cells, or production of an efficacy related gene pattern. The Examiner has taken the view that Mukherjee et al. discloses a correlation between the affinity of thiazolidinediones for PPARγ and the minimum effective dose required to lower glucose levels in diabetic rodent models and asserts that Mukherjee et al. is an application of the patent of Castle et al. to diabetes related drugs with the advantage of treating diabetic related complications. The Examiner then concludes that it would have been obvious to modify the toxicological algorithm of Castle et al. to determine and classify the activity of an agent by use of the PPARγ efficacy analysis of Mukherjee et al. because Mukherjee et al. has the advantage of exemplifying a correlation between the required agents, cell species, and the efficacy in treating diabetes related complications. Applicants disagree with the Examiner's conclusions for the following reasons.

It is submitted that the Examiner has failed to establish a *prima facie* case of obviousness because: (1) Castle et al. fails to teach or suggest the comparison of at least one of an efficacy

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value of an agent, a toxicity value of an agent or a classifier value of an agent to at least one of a reference efficacy value, a reference toxicity value or a reference classifier value to determine whether the agent possesses the defined biological activity and to determine the *degree of the defined biological activity*; (2) Castle et al. fails to teach or suggest the determination of an efficacy value or a classifier value of an agent; (3) as acknowledged by the Examiner, Castle et al. does not teach partial agonist activity with respect to a biological response, partial agonist activity with respect to PPARγ, use of 3T3L1 adipocyte cells, or production of an efficacy related gene pattern; and (4) Mukherjee et al. fails to cure the deficiencies of Castle et al.; therefore, even if improperly combined, the combination fails to teach or suggest every element of the claimed method.

As an initial matter, it is noted that Claim 1, from which Claims 8, 9, 13, 16, 17, 27, and 29 depend, has been amended as described above. As described above in connection with the rejection of Claim 1 under 35 U.S.C. §102(b), Castle et al. fails to teach or suggest the comparison of at least one of an efficacy value of an agent, a toxicity value of an agent or a classifier value of an agent to at least one of a reference efficacy value, a reference toxicity value or a reference classifier value to determine whether the agent possesses the defined biological activity and to determine the *degree* of the defined biological activity.

Moreover, it is noted that Castle et al. fails to teach or suggest the determination of an efficacy value or a classifier value of an agent. The Examiner has asserted "[t]he model of Castle et al. is used not only to determine agent toxicity, but also agent efficacy, by assigning the agent a classification such as that shown in Figure 1 of Castle et al." However, in contrast to the Examiner's assertion in this regard, it is noted that the teachings of Castle et al. appear to be directed only to toxicity profiling. For example, as stated in Castle et al., "[t]he present invention, a method and system for expression similarity profiling for *predictive toxicology*,

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employs a number of different methods for multivariate statistical analysis." Page 28, lines 12-14 (emphasis added).

Further in this regard, the Examiner has relied on an interpretation of Figure 1 of Castle et al. as "illustrating a) efficacy, b) toxicity, c) no effect and d) plateau effect of the agent." However, it is noted that the Examiner's interpretation of Figure 1 of Castle et al. does not derive from the teachings of the reference itself. As an initial matter, it is noted that Figure 1 of Castle et al. does not include any labeled axis. Moreover, the passages of Castle et al. that refer to Figure 1 merely refer to "patterns" that are "relevant to the toxicological process," as further shown below.

As stated in Castle et al.:

> [A]n aspect of the present invention is an analysis of the variance for each gene contrast analysis. In this gene contrast analysis, the response of a gene or set of genes is monitored upon exposure to a chemical. In one preferred embodiment, the response of a gene or set of genes to a chemical can be fitted into *one of four patterns illustrated in Figures 1a, 1b, 1c, and 1d.* In this preferred embodiment, upon classification into one of these four groups, an analysis is then performed which categorizes the gene contrast analysis as one or four summary scores.

Page 8, lines 10-17 (emphasis added).

As further stated in Castle et al.:

> . . . responses of a gene or set of genes to a chemical that fit into *patterns corresponding to either Figures 1a or 1b* are subjected to analysis which categorizes the gene contrast analysis as one of four summary scores. In such an embodiment, the input data are *genes selected from patterns that are biologically relevant to the toxicological process* . . .

Page 9, lines 3-7 (emphasis added).

Finally, as stated at page 10, lines 3-5, of Castle et al., "[I]n correlating these other studies, one preferably compare gene lists for *patterns of interest* between studies of related compounds to arrive at *a consensus set of genes involved in a toxicological response*" (emphasis

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added). Therefore, it is respectfully submitted that Castle et al. fails to teach or suggest the determination of an efficacy value or a classifier value of an agent.

In addition, as acknowledged by the Examiner, Castle et al. does not teach partial agonist activity with respect to a biological response, partial agonist activity with respect to PPARγ, use of 3T3L1 adipocyte cells, or production of an efficacy related gene pattern.

The teachings of Mukherjee et al. fail to cure the deficiencies of Castle et al. noted above. Mukherjee et al. describes the characterization of a novel PPARγ ligand (LG100641) that was *identified in a protein binding assay* (see page 1431) and does not teach or suggest the use of transcriptional expression profiling to determine whether an agent possesses a defined biological activity, as claimed.

In fact, it is submitted that the teachings of Mukherjee et al. would actually lead one of skill in the art away from the claimed method of the invention. As mentioned above, the novel compound LG100641 was initially identified as a PPARγ ligand in a protein binding assay. Upon further characterization, as described in the cited reference, Mukherjee et al. discloses the "identification of a compound, LG100641 that binds to PPARγ *but does not activate gene expression.*" Page 1425 (emphasis added). As further described in Mukherjee et al., "LG100641-bound PPARγ is *transcriptionally silent.*" Page 1429 (emphasis added). Therefore, it is submitted that the teaching of Mukherjee et al. would lead one away from the claimed method of the invention because there is no reasonable expectation of success provided for the use of transcriptional expression profiling to determine whether an agent possesses biological activity with respect to PPARγ. Accordingly, there is no motivation to combine the referenced teachings, and even if the teachings of Castle et al. and Mukherjee et al. were to be combined, which there is no suggestion or motivation to do, the combination does not teach or suggest all the elements of the invention as claimed.

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Therefore, in view of the above, it is demonstrated that the combination of Castle et al. and Mukherjee et al. does not render Claim 1 obvious, nor Claims 8, 9, 13, 16-17, 27, and 29, which depend therefrom. Accordingly, the Examiner is respectfully requested to withdraw this combination of references as a ground for rejection under 35 U.S.C. § 103(a).

New Claims

Claims 68-70 have been added. Support is found throughout the application as filed, for example, at page 38, lines 1-31.

CONCLUSION

In view of the foregoing remarks, applicants submit that all of the pending claims are in condition for allowance and notification to this effect is respectfully requested.

Respectfully submitted,

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